



ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ “Ο ΕΥΑΓΓΕΛΙΣΜΟΣ”
Α' ΚΑΡΔΙΟΛΟΓΙΚΟ ΤΜΗΜΑ



EVAGELISMOS GENERAL HOSPITAL OF ATHENS
A' DEPARTMENT OF CARDIOLOGY

January 2011 • Volume 6 • No 1 (21)

ISSN: 1792-7919

e-ISSN: 1792-7927

RHYTHMOS

Editor-in-Chief: Antonis S. Manolis, MD

*Editorial Staff: Spyridon Koulouris, MD, Sokratis Pastromas, MD, Ektor Anninos, MD,
 Ioannis Kontonassakis, MD*

Διευθυντής Σύνταξης: Αντώνης Σ. Μανώλης

Μέλη: Σπυρίδων Κουλούρης, Σωκράτης Παστρομάς, Έκτωρ Άννινος, Ιωάννης Κοντονασάκης

URL: <http://rhythmos.dyndns.org> / <http://rhythmos.info.tm> / <http://www.evangelismos.dom.gr>

EDITORIAL

Dabigatran: An Alternative to Warfarin After Over Half a Century

Antonis S. Manolis, MD

First Department of Cardiology, Evangelismos General
 Hospital, Athens, Greece

For over half a century, warfarin or other vitamin K antagonists (VKA) (such as acenocoumarol, available in Greece and other countries), have been the gold standard and the only oral anticoagulants available which have been shown to effectively treat thromboembolism.¹⁻³ However, their use has been plagued by inherent limitations with cumbersome monitoring via laboratory-guided adjustments of the dose, narrow therapeutic window, a lot of drug and food interactions and unpredictable and variable response. This has hindered patient compliance and has led to suboptimal therapy and poor anticoagulation control. Also patients unable or unwilling to take VKA have been offered no other choice of equivalent efficacy, i.e. until recently. Reasons for not receiving a VKA may comprise the following: drug allergy, patient refusal to take or decision to discontinue the drug, inability to maintain the international normalized ratio (INR) in the 2.0-3.0 range, physician decision as to the inappropriateness of receiving the drug, and/or inability to monitor the INR (lack of or difficulty in accessing a laboratory or lack of family support or assistance with this tedious task).

These hurdles of conventional anticoagulant therapy have spawned efforts to develop new medications that will surpass these drawbacks while matching the efficacy of VKAs.³⁻⁸ *Factor Xa* has a strategic role in the coagulation cascade, critically poised at the juncture of the contact activation (intrinsic) and the tissue factor (extrinsic) coagulation pathways proximal to thrombin, both activating the final common pathway and leading to fibrin formation. Active factor Xa hydrolyzes and activates prothrombin to thrombin. *Thrombin* is the most important constituent of the coagulation cascade and has a broad array of functions with a primary role in the conversion of fibrinogen to fibrin, the building structure of a hemostatic plug. Significant advances have been accomplished in the development of more specific agents targeting coagulation factors II (thrombin) or Xa and providing more predictable and stable anticoagulant responses by not interfering with diet, and having fewer interactions with other drugs. They also provide the convenience of oral administration with fixed dose regimens not necessitating routine monitoring with laboratory tests, all these having a positive impact on patient compliance. Novel oral agents like the thrombin inhibitor *dabigatran* etexilate and the factor Xa inhibitor *rivaroxaban*, have already become available for prevention of deep venous thromboembolism after orthopedic procedures, such as elective hip and knee arthroplasty, while other factor Xa inhibitors (*apixaban* and *edoxaban*) are being evaluated in phase III clinical trials. The initial results of the studies employing these new compounds are promising and provide evidence of improvement in

treatment of venous thromboembolism and in the prevention of stroke in patients with non-valvular atrial fibrillation.

The RE-LY trial has recently demonstrated that the oral direct thrombin inhibitor, dabigatran etexilate, is an effective alternative for oral anticoagulation with VKAs for stroke prevention in patients with atrial fibrillation.^{3,4} After initial failures with similar medications (e.g. ximelagatran, charged with liver dysfunction), these results constitute a breakthrough in anticoagulation therapy. In the RE-LY trial, in patients with atrial fibrillation and at least one additional risk factor for stroke, dabigatran 150 mg bid reduced both stroke and intracranial and life-threatening hemorrhage without any significant increase in overall major hemorrhages compared with warfarin, whereas the lower dose of dabigatran (110 mg bid) while non-inferior at reducing risk of stroke, it reduced intracranial, life-threatening, and major bleeding. Dyspepsia was a more frequent side-effect of dabigatran (11-12%) compared with warfarin (~6%). Importantly, dabigatran did not cause hepatotoxicity. However, a word of caution relates to the occurrence of bleeding while receiving dabigatran, as there is no specific antidote for this drug, which has a half-life of 12-17 hours. Supportive therapy for severe bleeding may include transfusions of fresh-frozen plasma, packed red blood cells, or exploratory surgery if indicated.

The American Food & Drug Administration (FDA) approved dabigatran on October 19, 2010 for anticoagulant use in patients with nonvalvular atrial fibrillation.⁵ However, only the higher dose (150 mg bid) was approved for patients with a creatinine clearance >30 mL/min. In patients with severe renal insufficiency (creatinine clearance 15 to 30 mL/min) half the dose (75 mg bid) was recommended, which however was not evaluated in the RE-LY trial. Dabigatran has also been approved in Canada and at least 12 other countries and awaits approval by the European Medicines Agency (EMA). Dabigatran (Pradaxa®, Boehringer Ingelheim) is the first new oral anticoagulant to become available for clinical use in over half a century.

Other novel oral anticoagulant agents next in line to receive approval for marketing for stroke prevention in patients with atrial fibrillation include the factor X inhibitors, rivaroxaban (Xarelto®, Bayer/Johnson & Johnson) which is an oxazolidinone derivative assessed in the ROCKET-AF trial and found to be non-inferior to warfarin,⁷ apixaban (Eliquis®, Pfizer / Bristol-Myers Squibb) evaluated in the AVERROES trial but only versus aspirin,⁶ while its comparison with warfarin in the ARISTOTLE trial is still pending,⁸ and edoxaban (Lixiana®, Daiichi Sankyo) which is being compared with warfarin in the ENGAGE AF TIMI-48 trial.⁸ The shorter half-life of these new agents will probably improve their safety profile, but, on the other hand, it

will also pose a risk of inferior protection if doses are missed. These new drugs are substrates for P-glycoprotein and they are metabolized by cytochrome P-450 3A4.⁸ Hence, caution is advised to avoid the concomitant use of drugs that inhibit these pathways, such as azole antifungal agents or protease inhibitors. Finally, the cost issue is very important, as the cost of these new agents will be much higher than that of VKAs, and needs to be factored into the decision-making process with any of the new anticoagulants.

REFERENCES

1. Ansell J, Hirsh J, Hylek E, et al. American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133 (Suppl 6): 160S-198S.
2. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005; 106: 1095-1106.
3. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;376(9745):975-983.
4. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139-1151.
5. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS Focused update on the management of patients with atrial fibrillation (update on dabigatran): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2011;57:1330-1337. *Circulation* 2011;123:1144-1150.
6. Connolly SJ, Eikelboom J, Joyner C, et al for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; 364:806-817.
7. Mahaffey KW, Fox KAA. Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). (http://sciencenews.myamericanheart.org/pdfs/ROCKET_AF_p_slides.pdf).
8. Hylek EM. Therapeutic potential of oral factor Xa inhibitors. *N Engl J Med* 2010; 363: 2559-2561.